CONCURRENT CHEMORADIATION WITH WEEKLY CISPLATIN AND DAILY CAPECITABINE FOLLOWED BY INTRACAVITARY BRACHYTHERAPY IN THE MANAGEMENT OF ADVANCED CERVICAL CANCERS A SINGLE ARM PROSPECTIVE STUDY

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CHENNAI – 600032

APRIL 2016

CERTIFICATE

This is to certify that **Dr.M.SENTHILKUMARAN** has been a Post Graduate MD Student during the period from May 2013 to April 2016 in the Department of Radiotherapy, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai.

This dissertation titled **"Concurrent chemoradiation with weekly cisplatin and daily capecitabine followed by intracavitary brachytherapy in the management of advanced cervical cancers"** is a bona fide work done by her during the study period and is being submitted to The Tamil Nadu Dr. M. G. R Medical University in partial fulfillment of the MD Branch IX Radiotherapy examination.

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DECLARATION

I solemnly declare that the dissertation titled "Concurrent chemoradiation with weekly cisplatin and daily capecitabine followed by intracavitary brachytherapy in the management of advanced cervical cancers ",a SINGLE ARM PROSPECTIVE STUDY was done by me at the Department of Radiotherapy, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai during March 2015 to August2015 under the guidance and supervision of Prof.Dr.N.VKALAIYARASI .

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CONTENTS

Concurrent chemoradiation with weekly cisplatin and daily capecitabine followed by intracavitary brachytherapy in the management of advanced cervical cancers

DR SENTHILKUMARAN.M, PROF DR.S.SHANMUGHAKUMAR, PROF DR.N.V.KALAIARASI, DR BASKAR, DR MADHUMATHI. DR PRABHAKARAN, DR SUNDARESAN, DR SANJALKUMAR, DR VIAY KARTHIK

Background

In developing countries most of the cervical cancer presents in advanced stage of disease Improving the therapeutic outcome of bulky cervical cancers is a big challenge addition of newer chemotherapeutic agents, to increase the cure rates of bulky cervical cancers.

Aims and Objectives:

To assess the clinical response rates and acute toxicity in the treatment of advanced cervical cancers with concurrent chemoradiation with weekly cisplatin and daily capecitabine followed by intracavitary brachytherapy.

Material & Methods

Single arm prospective study with 30 patients with locally advanced cervical cancer presented to Department of Radiotherapy, Madras Medical College, Chennai

Eligible patients to be treated with concurrent radiotherapy to the whole pelvis – 50Gy along with weekly cisplatin40mg and daily capecitabine300mg/sqm bd followed by intracavitary irradiation and assessed for response to treatment. The clinical response rates will be assessed after intracavitary irradiation.

RESULTS

Among the 30 patients majority of them were in the fourth decade .43% of the patient had stage IIB disease,56%of patient had IIIB disease overall complete response was 90%,with IIB disease CR [92%] IIIB disease CR[88%].100% CR in the subgroup with performance status >90 and age [31-40yrs].toxicities observed in the study were leucopenia grade 3 in 4 patients and grade 2 in 6 patients and diarrhoea grade 2 in 4 patients and grade 3 in 4 patients.

CONCLUSION

In the study patients with younger age , good performance status with IIIB disease had better response rate as they were able to complete CCRT schedule with manageable toxicities

Keywords: cervix, concurrent chemoradiation, cisplatin, capecitabine,

[Abstract]

INTRODUCTION

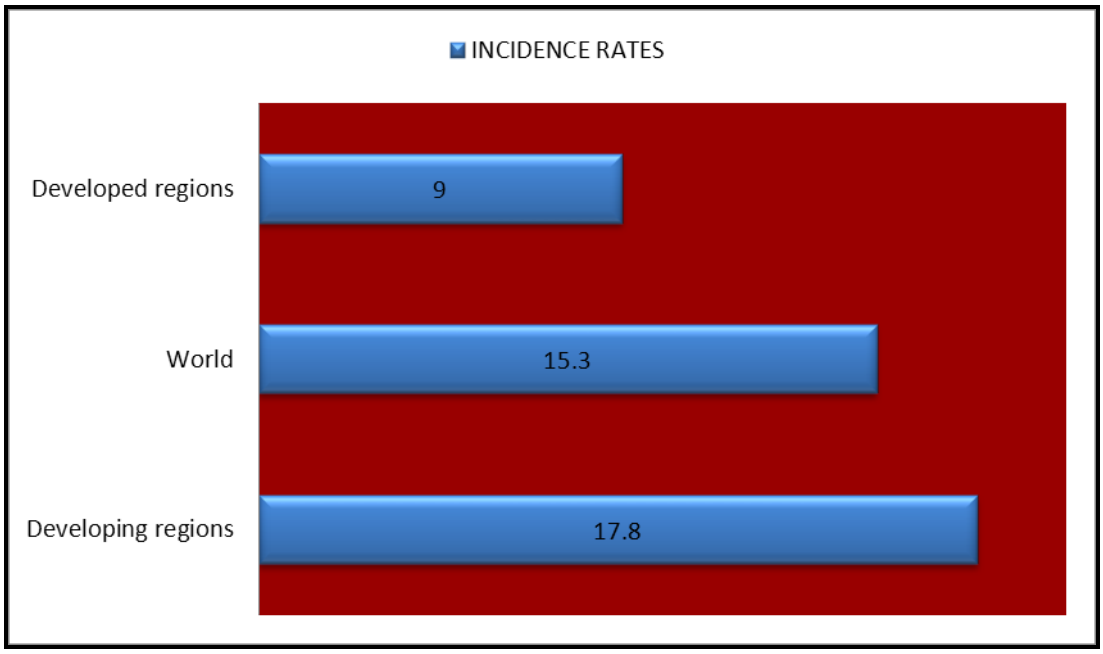
Cancer cervix is the second commonest malignancy among women globally, is the commonest malignancy to affect the female population in developing countries. During the past 5 decades the incidence of invasive cervical carcinoma has dropped dramatically which is attributed to the development of effective screening techniques for identification of pre-invasive lesions. The scenario, however, is still grim in the developing world wherein a combination of inadequate screening facilities, social stigma and ignorance contribute to patients presenting with locally advanced disease.

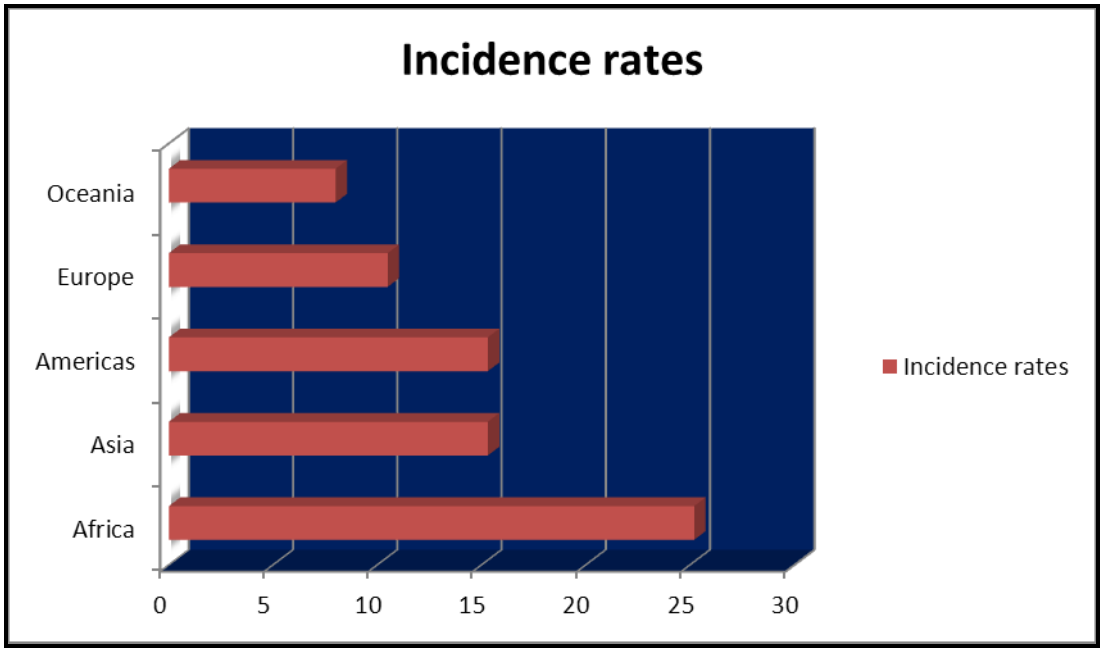
NATURAL HISTORY

INCIDENCE

The low risk regions are Western Asia, North America, Australia and Newzealand. The most common cancer in women in Eastern Africa, South-Central Asia and Melanesia is cervical cancer. Overall, the mortality: incidence ratio is 52%. The death due to cervical cancer is 275000 in 2008. 88% of deaths occurred in developing countries [1]. There is a seventeen fold variation in mortality between the different regions of the world [Yang et al].

World Age Standardized Incidence Rates of Cervical Cancer





CERVICAL CANCER BURDEN IN INDIA

In India, cervical cancer has been the most important cancer in women over the past few decades. India accounts for one fourth

of the global burden The incidence rates of cervical cancer is the highest in 2 out of the 12 Population Based Cancer Registries (PBCR). It has the second highest incidence rate after breast cancer in the rest of the PBCRs. Chennai has the highest age adjusted incidence rates whereas Thiruvanathapuram in Kerala has the lowest (National Cancer Registry Programme and World Health Organisation). North eastern districts of Tamilnadu show a higher incidence compared to other districts ICMR].

PBCR	CR	AAR
Bangalore	14.3	18.8
Barshi	20.0	22.8
Bhopal	12.0	17.7
Chennai	20.3	22.3
Delhi	12.3	17.4
Mumbai	11.5	13.9
Ahmedabad	6.9	7.9
Kolkata	13.2	12.3
Dibrugarh district	3.8	5.1
Kamrup urban district	12.8	17.3
Silchar town	10.6	12.1
Imphal west district	17.2	20.5
Mizoram state	13.7	17.4
Aizwal district	20.6	25.4
Sikkim state	6.9	10.9

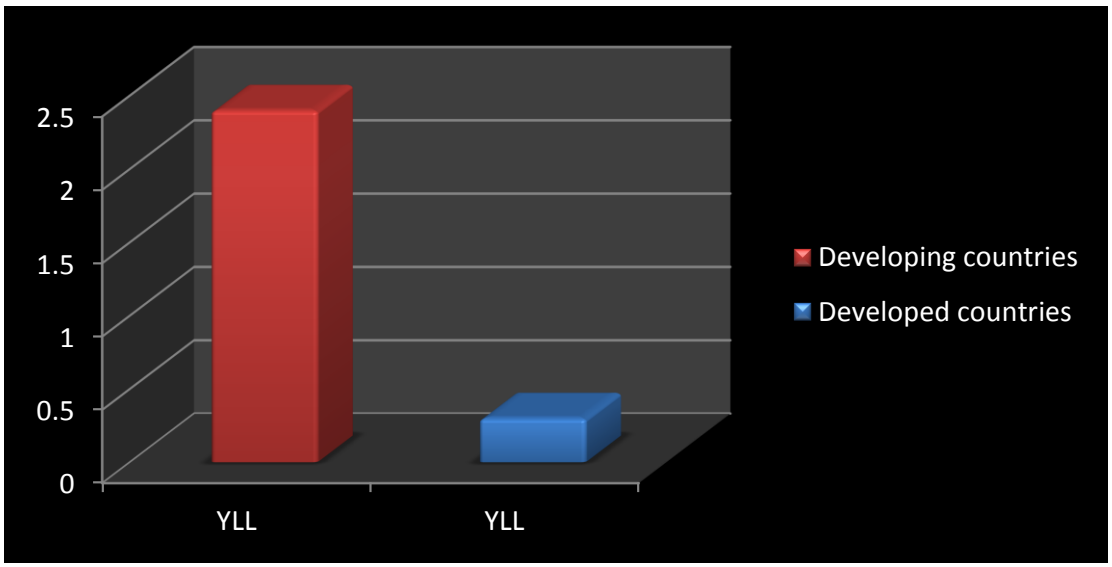
The burden of cervical cancer in India is disproportionately high Shanta etal]. The prevalence is much higher in rural India and among women of low socio economic status . This is due to lack of awareness of risk factors of the disease and lack of access to health care facilities. Compliance to, and follow up of, treatment is much worse for women of low socioeconomic status, leading to further morbidity and mortality from the disease . Despite having had a diagnosis of cervical cancer, around 40% of patients registered in the Hospital Based Cancer Registries in Bangalore, Chennai and Mumbai did not receive treatment at the reporting institution. Thus the burden of this debilitating disease is highest in the most disadvantaged sections of Indian society.

Cervical cancer is the third largest cause of cancer mortality in India after cancers of the mouth & oropharynx, and oesophagus, accounting for nearly10% of all cancer related deaths in the country. Among women, it is the leading cause of cancer mortality, accounting for 26% of all cancer deaths.Cervical cancer screening programmes have reduced mortality and morbidity from the disease in the developed world . However, these success stories are not applicable to developing countries because cytology based screening demands infrastructure, equipment and manpower. As a

result, death and disability from this cancer are high in low middle income countries, including India .

ECONOMIC BURDEN OF CERVICAL CANCER

Cervical cancer causes loss of productive life both due to early death as well as prolonged disability. It is responsible for 2.7million (age weighted) Years of Life Lost (YLL) worldwide among women between the ages of 25 and 64, out of which 2.4million occur in developing areas The Years of Life Lost (YLL) due to cervical cancer is greater than that caused by any other cancer in India. It accounts for 4% of total YYLs due to all causes in India. In India, the Years of Life Lost (YLL) due to cervical cancer were 936.3 in 2000, being among the highest in the world [Yang et al].



This mortality burden poses a heavy economic burden on families as well as the country because women aged 25 – 64 years, tend to be the sole caretakers of the house and in some cases they contribute significantly to the family income. Additionally, the high medical costs that are incurred by families due to cervical cancer (especially since most cases in developing countries are diagnosed at advanced stages when treatment is costly but prognosis poor),further impoverish individuals and communities [Bishop et al].

Hence it becomes imperative to identify new prevention strategies to reduce the risk of cervical cancer overall, to design new methodologies to detect cancer early and to explore newer treatment options to improve the therapeutic outcome of cervical cancers.

RISK FACTORS FOR CERVICAL CANCER

1. Female sexual behavior

- Sexual intercourse - This is the major prerequisite for the development of cancer cervix
- Age at first intercourse - Women who start their sexual life at an early age particularly before 16 years are at higher risk

(2.4 fold increased risk) of developing cancer cervix [Agarwal et al]

- Multiple sexual partners - Cancer cervix patients usually give a history of multiple sexual partners. The risk is doubled for women with 6 sexual partners.

Parity - Risk factors related to parity include first childbirth at an early age and multiparity.

2. Male sexual behavior (high risk male)

High risk male sexual habits, the presence of which is associated with a higher incidence of cancer cervix in their spouses are

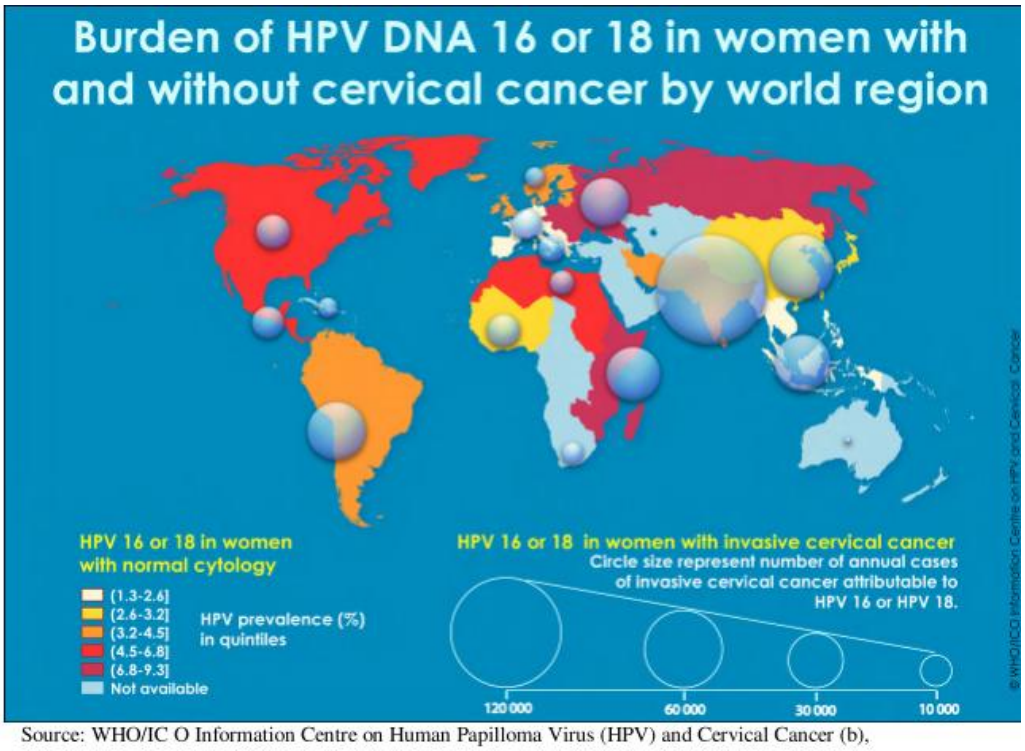
- Sexual promiscuity: >3 extra marital partners
- History of sexually transmitted disease
- History of cancer penis (increases risk of cancer cervix in wife by 3 – 6 times)
- History of cancer cervix in first wife (increases risk of cancer cervix second wife 2 fold)
- Poor penile hygiene, Causative role of cigarette smoking in male and the protective effect of male circumcision are controversial.

3) Lower socio-economic group

Women from a lower socio-economic group have a higher incidence (about 3 fold)of cervical malignancy due to early marriage, early onset of sexual life and lack of genital hygiene.

4) Viral etiology

- HPV (Human Papilloma Virus) - Among various agents, the HPV virus is considered to be the most likely candidate for etiological responsibility. Infection with HPV serotypes16 & 18 are highly prevalent in CIN-II, III and invasive cancer cervix. HPV exerts its effect by P-53 gene suppression and inhibition of cell mediated immunity.



Source: WHO/IC O Information Centre on Human Papilloma Virus (HPV) and Cervical Cancer (b),

- HIV (Human immunodeficiency virus) - Women who are HIV positive have a 10 fold risk of cervical cancer in comparison with matched controls. Prevalence of cancer cervix in HIV positive patients below the age of 50 years is 19%.

- HSV (Herpes simplex virus) - There is much data suggesting an association between cancer cervix and HSV but no conclusive proof is available.

5). Smoking

Smoking appears to double the risk of developing cervical cancer [Gram et al]. Smoking constituents have been detected in cervical mucus. Levels of nicotine were increased forty-fold and the major metabolite of nicotine, cotinine levels were increased four-fold in the cervical mucus of women with CIN, compared to serum levels[Hellberg et al]. It was found that there was increased DNA damage in cervical epithelium of smokers, regardless of concomitant HPV infection[Simons et al].

FIGO STAGING

0 No evidence of primary tumor; Ca in situ

Cervical Ca confined to uterus

1A Invasive Ca diagnosed only by microscope

A1 Stromal invasion not greater than 3 mm the depth and 7mm horizontal spread

A2 Stromal invasion >3 mm and not more than 5 mm with 7mm or less horizontal spread.

IB Clinically visible lesions confined to Cervix or microscopic extension >1A

B1 Visible lesion 4cm or less in greater dimension

B2 Visible lesion > 4cm in greatest dimension

II Tumor invades beyond uterus but not to pelvic wall or lower 1/3 vagina

IIA No obvious parametrial involvement. Involvement of as much as the upper two thirds of the vagina

IIA1 less than or equal to 4cm

IIA2 >4cm).

IIB Obvious parametrial involvement but not onto the pelvic sidewall.

III Tumor extends to pelvic wall or involves lower 1/3 vagina causes hydronephrosis or non functioning kidney

IIIA Tumor involves lower 1/3 vagina not extending to pelvic wall

III B Tumor extending to pelvic walls or causing hydronephrosis or non functioning kidney

IV Tumor invades the mucosa of the bladder and rectum and or extends beyond the true pelvis

IVA Tumor invades the mucosa of bladder &rectum or extends beyond true pelvis

IVB Distant metastasis

PROGNOSTIC FACTORS

Identification of factors of possible prognostic significance may help the clinician in tailoring treatment. Patients with a low risk of recurrence may be subjected to less intensive treatment whereas patients with a high risk of recurrence may be eligible for clinical trials.

TUMOR FACTORS

Stage of the disease has been found to be a strong prognostic factor. As the disease advances, the prognosis becomes worse. Numerous studies have indicated tumor size as a strong prognostic indicator for both early and locally advanced cervical cancer.

Tumor size more than 4 cm has been defined as bulky cervical cancer by FIGO and 10 year actuarial pelvic failure rates are found to be higher in patients with bulky cervical cancers. Another strong prognostic indicator is depth of invasion. Lympho vascular space invasion is a classical prognostic parameter in early stage cervical cancer. Presence of lymph node metastases has been proven to be of prognostic importance in several studies. In early stages, the depth of tumor invasion determines the incidence of pelvic lymph node metastases and in advanced stages, tumor volume determines the incidence of lymph node metastases.

The extent of parametrial involvement was found to orrelate adversely with survival. A retrospective study done by Kovalic et al, reported lower 10 year disease free survival for patients with stage IIB disease with lateral half of parametrial involvement compared to medial half of parametrial involvement (52% Vs 68%, p value = 0.004). Stage IIB patients whose disease extended into the lateral parametrium had higher total pelvic failure rates.

The 10 year disease free survival was lower in patients with stage IIIB cancers with bilateral parametrial invasion compared to unilateral parametrial invasion [Kovalic et al].

EXTENT OF PARAMETRIAL INVOLVEMENT AND PROGNOSIS

Stage	Extent of parametrial disease	Survival (10 yr DFS)
II B	Unilateral involvement	64%
II B	Bilateral involvement	61%%
III B	Unilateral involvement	50%
III B	Bilateral involvement	34%

A patient care evaluation study of the American College of Surgeons on 11,157 patients reported no significant difference in 5 year survival among patients with squamous cell carcinoma, adenocarcinoma and adenosquamous carcinoma [Hugh et al]. However there are conflicting reports in the literature regarding the importance of histologic subtype as a predictor of overall survival in patients with cervical cancer. In contrast to other epithelial malignancies where histologic grading is an established prognostic factor, microscopic grading of cervical cancers have no prognostic value [Smiley et al]]

Overall treatment time is a critical parameter which determines treatment outcome. Loss of local control and survival of 1% per day when treatment exceeded 52 days has been reported in studies [Girinsky et al].There is controversial data in the literature

regarding the relationship of HPV genotype to prognosis in cervical cancer. However recent evidence suggests that HPV 18 positive cancers are associated with poor prognosis [Trimble et al]. Elucidation of the mechanism involved in such association could lead to newer treatment approaches.

HOST FACTORS

An association between lower socioeconomic status and poorer survival has been reported in several studies. Poverty and lower education has been associated with increased cervical cancer mortality [Murphy et al].

DEATH RATES BY RACE

Race	Female
White	2.2 per 100,000 women
Black	4.3 per 100,000 women
Asian/pacific islander	2.0 per 100,000 women
American Indian/ Alaska Native	3.5 per 100,000 women
Hispanic	3.0 per 100,000 women

SEER Stat Fact Sheets: cervix uteri

In multivariate analysis, hemoglobin levels at the time of diagnosis were associated with worse overall and disease free

survival. The impact of declining hemoglobin level during Radiotherapy on the final outcome was not observed in multivariate analysis [Serkies et al].

Smoking is a predictor of worse overall survival in patients with locally advanced cervical cancer treated with chemoradiation. Median survival was found to be 15 months shorter for smokers . Smoking was linked to increased cervical cancer mortality in 3 of 5 survival analysis. A recent report found that smokers with high risk HPV positive cervical cancers were four times more likely to die of cervical cancer [Wright et al].

TREATMENT PRINCIPLE WITH RADIATION

Ionizing radiation can kill cells which are actively replicating by two methods:

1) Apoptosis or programmed cell death - where cells die immediately without dividing.

2) Reproductive cell death - irreversible loss of reproductive integrity.

These effects are brought about by the direct and indirect effects of radiation on cells where the DNA is the predominant cellular target. Direct effect of radiation - Here the ionising

radiation interacts directly with the critical target molecules in the cells (the DNA) causing excitation and ionization leading to biochemical lesions which lead to reproductive death of cells. The different types of lesions produced by radiation within the nucleus include – Single or double strand breaks, Base damage and Cross links.

Indirect effect of radiation - Here the radiation produces biological damage indirectly through the formation of free radicals which are generated by water hydrolysis. The most common free radicals generated include hydroxyl ions, hydrogen ions, hydrated electrons and hydrogen peroxide. The damage produced by free radicals is promoted by the presence of O_2 expressed as the oxygen enhancement ratio (OER) and decreased by the presence of free radical scavengers like sulphydryl compounds.

FACTORS INFLUENCING THE EFFECTS OF RADIATION

The effects of radiation on the cells are influenced by the following factors

1) Dose

2) Dose rate

3) Radiation quality expressed in terms of LET and RBE

4) Repair of sub-lethal and potentially lethal damage

5) Phase of cell cycle - Maximum cell kill due to radiation is obtained when cells are irradiated in the G_2 and M phases of the cell cycle. The radiosensitivity decreases during the G_1 and early S phase and the late S phase is the most radioresistant phase in the cell cycle.

6) Radiation fractionation - Based on the principles of repair, reoxygenation, repopulation and redistribution.

7) Presence of O_2 or free radical scavengers.

OVERVIEW OF TREATMENT POLICY IN CANCER CERVIX

All the three standard modalities of oncology namely radiation, surgery and chemotherapy have stamped their role in the treatment of different stages of the disease.

ROLE OF SURGERY IN CANCER CERVIX THERAPY

The role of radical surgery is limited to pre-invasive and early stages of invasive growth. In some selected cases it is combined with RT and it is used as a salvage procedure to treat local failure after RT.

In early disease surgery is preferred over RT in:

1) Small volume disease (<4cm)

2) Young patients for better preservation of sexual life in comparison to RT

3) Endocervical cancers and adenocarcinomas

4) Patients with co-existing diseases like uterus, ovarian cysts and prolapse.

ADVANTAGES OF SURGERY IN EARLY DISEASE

Surgery has the following advantages over RT in early disease:

- Surgery is both therapeutic and a staging procedure. Based on findings in the post-op specimen appropriate post-op RT can be combined to enhance cure rates.

- Surgery preserves the ovaries if necessary and leaves behind a pliable vagina which preserves the sexual life of the patient.

- Psychological relief to the patient that the disease has been cured is higher with surgery.

ROLE OF RT IN THE THERAPY OF CANCER CERVIX

Right from the time of its discovery nearly a century ago, radiotherapy has been the predominant modality used in the therapy of cancer cervix. Radiation finds a place in the management of all stages of the disease. In early disease it is an effective curative alternative to surgery. In locally advanced disease it is the primary curative modality. In metastatic disease radiation palliates local and distant complications. Radiation is delivered as brachytherapy alone, as ICA (intra cavitary application) in stage I disease or with ideally sequenced combinations of external beam radiation (EBRT) and brachytherapy in other stages. As the size of the lesion and the proportion of the cervix involved increases, the risk of lymph node involvement also increases and one has to irradiate the whole pelvis, covering the primary tumor, its local extension within the pelvis and the pelvic lymph nodes in contiguity.

A homogenous dose distribution over such a large volume can be achieved only by teletherapy. The external beam radiation is followed by ICA to achieve the highest local control rate possible and this sequence is also ideal in that the tumor shrinkage caused by the initial EBRT will bring the anatomy to near normal resulting in an optimal and uniform dose distribution from a subsequent ICA.

EBRT is delivered before brachytherapy in patients with bulky primary tumors, exophytic bleeding tumors, necrotic or infected tumors and tumors with parametrial involvement.

PRINCIPLE OF EBRT

EBRT aims at producing a homogenous dose to the target volume which includes the primary tumor (uterus with cervix), paracervical and parametrial tissue, vagina if involved and regional lymph nodes.

PRINCIPLE OF ICA

ICA delivers a very high dose to the central tumor volume including the cervix and adjacent tissues with maximum tumor control without crossing the tolerance of surrounding normal tissue. This is possible because the normal uterus and vaginal vault are relatively radio-resistant and tolerate relatively high doses of radiation and there is a rapid fall of dose at a distance from the cervix protecting the rectum, bladder and small bowel.

The normal tolerance doses of various organs included in the treatment field are as follows

Uterus with cervix	: 200 - 300Gy
Vagina	: 160 - 200Gy
Bladder	: 80Gy
Rectum	: 70Gy

The tolerance of the rectum and bladder are the critical dose limiting points in the radiation of cancer cervix.

DOSE REFERENCE POINTS

In intra-cavitary applications the dose is prescribed to specific points in the pelvis namely.

1) Point A: connect a line through the center of each ovoid or the lateralmost dwell position in the ring; extend this line superiorly along the radius of the ovoids (or ring), and then move an additional 2cm superior along the tandem. From this point, extend out 2 cm on each side laterally on a line perpendicular to the tandem

2) Point B – Defined as a point lying 3cm lateral to point A i.e 5cm lateral to centre of the cervical canal and 2 cm above the external os. This point represents the dose received by the obturator node and hence is the dose prescription point for the parametrium.

3) Bladder point – The bladder point is located using a Foley's catheter with the balloon filled with 7cc contrast material and distilled water. In the frontal simulation film the bladder point is marked at the centre of the balloon. In the lateral film the bladder

point is marked on the posterior end of a line drawn antero-posteriorly through the centre of the balloon.

4) Rectal points – Three rectal points are identified on the frontal simulator radiograph R_1 is the centre of a line joining the midpoint of the vaginal ovoids.R_2 and R_3 1cm above and below. On the lateral film the rectal points are identified on the horizontal line drawn from the middle of the ovoids to 5mm behind the posterior vaginal wall, 1cm above and below. The posterior vaginal wall may be identified by radio opaque gauze used for vaginal packing and rectum by rectal marker. The maximum dose received is calculated as rectal dose.

5) Pelvic wall points – In the frontal simulator radiograph the pelvic wall point is identified at the point of intersection of a horizontal tangent drawn to the superior aspect of the acetabulum. On the lateral film this point is marked as the highest mid-distance point of the right and left acetabulum.

A rectal probe is inserted to measure the dose received at the anterior rectal wall. This should be less than 60% of the dose received at point A. Computer generated isodose curves provide the best method of determining the doses to these various points.

RT REACTIONS

Early Reactions: Include radiation proctitis, cystitis and ileitis. Usually they are mild and transient. Skin reactions vary from erythema, dry desquamation to moist desquamation and ulceration.. Skin morbidity can be totally avoided by proper radiotherapeutic techniques.

Late Reactions: 5-10% of patients develop long term complication. Rectum or sigmoid colon may develop ulcerations or strictures. Fistulas are rare. Small bowel injury may result in persistent or intermittent attacks of diarrhea. Occasionally localized structures or perforations can occur, requiring pelvic surgery. Small bowel late reactions are more in patients with history of previous bowel surgery due to fixed bowel syndrome. The bladder morbidity usually manifests as repeated and self limiting attacks of haematuria. Vesico-vaginal fistula is usually secondary to bladder involvement by tumor. Hydronephrosis appearing for the first time after treatment is usually due to recurrent disease.

ROLE OF CHEMOTHERAPY

Initially chemotherapy was considered only in stage IV B disease to provide palliation of systemic disease. Combination of chemotherapy concurrently with radiation in locally advanced

cancer cervix is the present day rule. Recurrent cervical cancer after hysterectomy generally treated with radiotherapy alone has also been the subject of chemoradiation trials.

As the stage and tumor bulk increases the survival rates worsen. Despite significant technological advances, radiation alone has not produced significant local control rates in locally advanced cancer cervix. The rates of post RT residual and recurrent disease continue to remain high.

The reasons limiting the ability of RT producing desirable local control in locally advanced cancer cervix include increasing bulk of the primary lesion leading to poor tumor geometry, central hypoxia and low growth rate fraction. In the absence of local control these tumors lead to progressive pelvic disease, extra pelvic disease and finally death.

Thus the survival rates are pretty poor in locally advanced cancer cervix in comparison with early disease. Improved local control is necessary to achieve significant improvement in survival.

RATIONALE OF CONCURRENT CHEMORADIATION

The primary rationale of chemoradiation is

- Established limitation of single modality treatment

- The desire to improve results of such therapy

The various types of interaction could be

- Spatial co – operation
- Enhancement
    - Supra – additive
    - Additive
    - Sub – additive
- Diminution
    - Inhibition
    - Anatagonism

RADIOBIOLOGICAL MECHANISMS OF INTERACTION

Chemotherapy when combined with radiation leads to enhanced cell kill by the following mechanisms:

1. Inhibition of sub – lethal damage repair: Sublethal damage inflicted by radiation is reparable. The chemotherapeutic agents used in chemoradiation therapy interact with cellular repair mechanisms and inhibit repair, thereby enhancing tissue response to radiation.

2. Cell phase Re- distribution: Some drugs can block transition through mitosis with the result cells accumulate in G_2 and M phases, the most radiosensitive of the cell cycle leading to enhanced cell kill. Elimination of radio-resistant S phase cells by chemotherapeutic agents is another strategy.

3. Effects on tumor size and vascular supply: The effect of both modalities is inversely proportional to tumor size. When given concurrently, one modality reduces the tumor size and the other acts with increased efficiency.

4. Effect on repopulation: The " accelerated repopulation" is the result of compensatory regenerative response caused by cytotoxic action of chemotherapeutic drugs or radiation. Any approach that reduces or eliminates clonogen repopulation in tumors would improve radiation response. Chemotherapeutic drugs, as a result of their cytotoxic or cytostatic activity can reduce rate of proliferation when given concurrently with radiation therapy and hence increasing the effectiveness of treatment.

5. Effect on hypoxic and low pH cells: The effect of hypoxia is particularly pronounced in cancer cervix with regards to its response to radiation therapy .The presence of hypoxia makes

tumors more aggressive and more resistant to radiation as well as to most chemotherapeutic agents. Combining chemotherapeutic agents with radiation therapy can reduce or eliminate hypoxia or its negative influence on tumor radio-response. Most chemotherapeutic agents kill proliferating cells which are primarily found in well oxygenated regions of the tumor. Destruction of tumor cells in these areas leads to an increased oxygen supply to hypoxic regions and hence re-oxygenates hypoxic tumor cells making them more susceptible to radiation. Certain drugs that act in the acidic state of the tumors can also be used.

6. Modification of apoptosis: Apoptosis is a major dynamic process by which radiation induces cell death. Certain drugs can enhance cell kill through apoptosis.

BIOLOGICAL BASIS FOR FRACTIONATION

From those experiments it was evident that the benefits of fractionation were due to four factors

1) Repair
2) Reassortment
3) Repopulation
4) Reoxygenation

MODELS OF FRACTIONATION

1) The strandquist Plot

2) The nominal standard dose system (NSD)

3) The linear quadratic model

Now a days the linear quadratic model is being followed. The L-Q model explains that the radiation cell kill has two components. The initial linear component, which is due to single track events, and the quadratic component is due to two track events.

The linear component is denoted by $-\alpha D$ and the exponential component by $-\beta D^2$. P (Survival) = $e^{(-\alpha D-\beta D2)}$ where D is the total dose and α, β are constants which represents linear and quadratic components of cell kill respectively.

The linear quadratic model explains why there are different responses between tumor, early responding and late responding tissues. Here the tumor resembles early responding tissues in response to radiotherapy. By dividing total dose into number of fractions preferentially reduces the late effects.

Conventional fractionation means giving five fractions per week with dose 1.8 to 2Gy per fraction.

PHARMACOLOGY OF CISPLATIN

CDDP (CIS- CHLORO- DIAMINE- PLATINUM)

Cisplatin the platinum in each of these compound induces cell killing effect by the development of covalent bifunctional DNA adducts with cellular DNA. The cisplatinum contains two amines and two chloride group .cisplatin is given as single agent and also in combination with other drugs.

It is administered as IV infusion 50-75mg/m^2 given every 3-4 weeks or weekly 40mg/m^2.It is given as infusion in 250ml of normal saline in a duration of 1-4hrs . when infusion time is shorter there is more of clinical toxicity .Before infusion of cisplatin patient should be adequately hydrated About 2liters of IV fluid should be given .Mannitol 125mg is mixed with cisplatin in 250ml of normal saline .

Common toxicity from cisplatin is renal insufficiency with cation wasting nausea, vomiting, perirpheral neuropathy, auditory impairment, myelosuppression with low platelet count.Aggressive premedication for nausea is necessary before cisplatin therapy .5Hydroxytryptamine receptor antagonist, dexamethasone are given before chemotherapy to prevent vomiting.

5 FLUORO- URACIL

The fluoropyrimidine shows a broad activity against a range of solid tumors as GI malignancy (esophageal, gastric, pancreatic, colorectal, anal and hepatocellular), head and neck, ovarian carcinoma.

By the uracil transport mechanism 5FU enter the cells forms cytotoxic nucleotides by biochemical pathways and causes inhibition of thymidine synthase and also incorporated in RNA and DNA leading to genotoxic stress and cell death. 5FU is not administered orally as the bioavailability is erratic due to high level of catabolic enzymes DPD(dihydro pyrimidine dehydrogenase). dihydro pyrimidine dehydrogenase is higher in the gut mucosa .

5FU is eliminated rapidly. Half life is 8-14 minutes . 3 to 5% of the genral population has a partial or complete deficiency of DPD. When there is deficiency of the enzyme then they may have severe toxicity in the form of myelosuppression, diarrhoea, mucositis, and neurotoxicity.

CAPECITABINE

Capecitabine a oral fluoropyrimidine carbamate . capecitabine is extensively absorbed by the gut mucosa . The oral bioavailability is 80%. 5-deoxy 5 fluorouridine isconverted to 5FU

by thymidine phosphorylase. Thymidine phosphorylase level is higher in the tumor than normal tissue so there is increased availability 5FU in the tumor tissue there by increasing the efficacy of 5FU and reducing the toxicity .

Capecitabine is mainly excreted by kidney . Toxicity of capecitabine is as of 5FU myelosuppression, neutropenic fever mucositis and alopecia.

LITERATURE REVIEW

The role concurrent chemoradiation in cancer cervix has been under investigation by the Gynecological Oncology Group since the early 70s. The early studies were done with hydroxyurea as a radiosensitise . The combination of cisplatin with radiation in the treatment of cancer cervix lead to better local control and reduced distance metastasis This paved the way for further studies with cisplatin based chemoradiation

GOG-85 Whitney et al study was done in FIGO stage IIB to IVA(negative paraaortic nodes after dissection).In the investigational arm along with EBRT patients were given cisplatin50mg/m^2(D1&D29)+5FU4gm/m^2 .In the control arm along with EBRT hydroxyurea 80mg/m^2 was given twice weekly. The survival at eight year followup was 55% in the EBRT with cisplatin and 5FU arm verses 43% in EBRT with hydrxyurea arm. local control and survival were superior in the investigational arm. [1]

In GOG-120 Rose et al study eligibility criteria was FIGO stage IIB to IVA . In Arm1 cisplatin40mg/m^2 given weekly,in Arm2 cisplatin 59mg/m^2 (D1&D29) + 5FU 4g/m2- over 96hrs+ hydroxurea 2gm/m2 twice weekly for 6weeks was given with

EBRT. In the control arm hydroxyurea 3gm/m2 twice weekly along with EBRT. The 5year survival was 60% with cisplatin, 61% with cisplatin+5FU+hydroxyurea and 40% with only hydroxyurea along with radiation. The result shows cisplatinbased chemoradiation regimens improves over all survival. [2]

In GOG123 Keys et al women with bulky (>4cm)stage IB carcinoma cervix with radiographically or surgically negative pelvic or paraarotic nodes treated with pelvic EBRT and brachytherapy, followed by extrafascial hysterectomy .Trial arm received EBRTand brachytherapy with weekly cisplatin40mg/m2 and control arm treated with RT alone.the overall survival rates were (78%) trial arm and (64%) control arm.[3]

RTOG 90-01 Efiel et al conducted a study of 389 patients with stage IB to IIA of >5 cm with proven positive pelvic lymph nodes, or stage IIB to IVA carcinoma cervix treated in the trial arm with RT and concomitant chemotherapy with cisplatin (75 mg/m2) and 4-day infusion of 5-FU (1,000 mg/m2per day) and control arm with only RT.Overall survival rate for women on the trial arm(irradiation and cisplatin/5-FU) 67% versus 41% in the irradiation only arm.[4]

Southwest Oncology Group 8797 conducted a study for women with FIGO stage IA2, IB, or IIA carcinoma cervix with metastatic disease in the pelvic lymph nodes, positive parametrial involvement, or positive surgical margins at the time of primary radical hysterectomy with total pelvic lymphadenectomy.In the trial arm patients were treated with pelvic EBRT with 5-FU infusion and cisplatin, and control arm were treated with irradiation alone. 5-year overall survival of 80% (pelvic EBRT with 5-FU infusion and cisplatin arm) versus 66%(irradiation alone arm) favoring postoperative chemoradiation in high-risk patients.[5]

A 2005 update of a meta-analysis of CCRT and RT found 24 trials and concluded that chemoradiation improves overall survival (absolute benefits of 10%) and progression-free survival (absolute benefits of 13%) whether or not cisplatin was used [6]

A 2008 meta-analysis of the 13 trials that compared CCRT to RT found there was a 6% improvement in 5-year survival with CCRT. The effect was attributed to a reduction in both local and distant recurrence.[7]

The current standard of care for bulky stage cervical cancer is concurrent chemo radiation. The 5 year survival of stage IIB

cancers reported by GOG85/GOG 120 studies is between 60 to 70%, whereas RTOG 9001 reported a 5 year survival of around 75% for stage IB and IIB cancers. The results of the above studies imply that there is still room for improvement.

A study with FIGO stage IIB, IIIA, IIIB, and IVA. Patients were treated with external beam radiotherapy of 46Gy. Intracavitary high dose brachytherapy was given weekly. So that point A received a dose of 30Gy . cisplatin was given 30mg/ m^2 . every week along with external beam radiotherapy . There was complete response in 88% of patients at one year follow up . At four year follow up the survival was 65% and 24% patients failed distally . there was increased rate of GI toxicity . The study concluded that weekly cisplatin with external beam radiotherapy is a effective regimen in locally advanced cancer cervix. [Sauhami et al] [17]

Study with FIGO stage IB, IIA , and IIB Patients were treated with cisplatin 40mg/m^2 weekly and RT. Another arm were treated with only RT . At 5 year follow up the survival rate was 59% in the chemoradition radiation arm . Only RT arm it was 56% . but the late morbidity was higher in the chemoradiation arm.

This was the only trial that didnot show survival benefit with chemoradiation . The possible explaination for no survival benefit with chemoradiaton was it was a small trial compared to other chemoradiation trials and many patients were in early stage of disease,there by reducing thesurvival advantage of the chemoradiation arm compared to the only RT arm . [Pearcey et al][7]

PATTERN OF FAILURE IN BULKY CERVICAL CANCERS

Generally, optimizing primary treatment could be more rewarding than a deliberate post-treatment surveillance or aggressive salvage therapy. Locally advanced bulky cervical cancer is characterized by poor local control. As the tumor size increases, the risk for central disease recurrence is high [23].

The recurrence risk rate peaks in the first year of follow up but the hazard rate comes down after 3 years of treatment. However, the risk of central disease recurrence beyond three years continues to be greater for patients with bulky tumors . Hence, tumor size is an important determinant of treatment outcome in bulky cervical cancers[Thomas et al].

Cisplatin is the cornerstone in most of the chemoradiation regimens used in cervical cancer.5FU was used with cisplatin in the GOG trial was associated with a higher frequency of Grades 3 and 4 toxicity compared to weekly cisplatin. Administration of 5FU required admission and prolonged hospital stay .now we have the advantage of oral 5FU in the allowing out patient treatment

THE RATIONAL CISPLATIN AND CAPECITABINE WITH RADIATION IN THIS PRESENT STUDY ARE

Mechanism of interaction

Cellular hypoxia, cell cycle age distribution, intrinsic radio sensitivity of the tumour are important factors that determine the sensitivity of the tumour to radiation.

Hypoxia

Radiation kills the cancer cells by generating reactive hydroxyl free radical with the cellular water. In the presence of oxygen, the reactive free radical will react with the DNA strand, resulting in permanent DNA damage. Oxygen will supply electron to the damaged DNA strand and destabilize the strand break. This enhancement effect of oxygen in radiation therapy is known as oxygen enhancement ratio. Without the electron supply from oxygen under hypoxic condition, the DNA damages induced by radiation could be repaired by the cancer cells.

Chronic hypoxia will lead to amplification of certain oncogenes like ras, c- myc, c-raf-1 which are responsible for increased resistance to radiation. Also the radiation generates oxygen free radicals which damages DNA. It is also postulated that due to hypoxia chemotherapy drug diffusion distance is increased. This causes decreased amount of chemotherapy drug to enter the actively dividing tumor cells.(21)

Thus by combining radiation with a chemotherapeutic drug which is active against hypoxic cells, we can overcome this resistance to radiation. Cisplatin is active against hypoxic cells. Also Capecitabine metabolism's the main key enzyme Thymidine phosphorylase expression is increased in hypoxic conditions.

Cisplatin alkylates the DNA cause intrastrand and interstrand breaks, thereby makes it more vulnerable to radiation. It not only increases the damage caused by radiation but also inhibit repair of the radiation damage. Cisplatin inhibits the repair of sub lethal damage(SLD) and potentially lethal damage(PLD). It also causes inhibition of cell repopulation and modification of the slope of dose response curve.

The sensitivity to radiation varies widely depending upon which phase of the cell cycle, the cell lies. The G2 and M phase are three times more sensitive to radiation than S phase. The S phase is the most radioresistant phase followed by early G1 phase. The exact mechanism for this is not known. This mechanism is exploited therapeutically in concurrent chemo radiation strategies.

Most of the chemotherapeutic agents kill proliferating cells which are situated in the well oxygenated area. These areas lies close to capillaries hence they are easily accessible to chemotherapeutic agents. When these proliferative cells are killed, the bulk of the tumour is decreased and the interstitial pressure falls. This result in opening of closed capillaries and previously hypoxic cells become oxygenated. Since the tumour shrinks, the previously hypoxic areas move nearer to capillaries.

Finally the loss of oxygenated cells results in more availability of oxygen to previously hypoxic cells which become oxygenated and susceptible to radiation. Tumour cells have accelerated cell proliferation, hypoxia and acidity which are not present in normal cells.

The expression of the enzyme thymidine phosphorylase is increased in conditions with hypoxia, poor perfusion and acidosis. This is the condition in most of the solid tumors .

Due to the preferential activation the enzyme thymidine phosphorylase, Capecitabine concentration inside the tumor cell is higher compared to the normal tissues. Also the concentration of Capecitabine is higher than that of infusional 5FU, Capecitabine treatment leads to 2.9 times higher concentration of 5 FU in the tumor cell compared to non-malignant tissues. (45, 50)

Study was done to find the role of thymidine phosphorylase, an angiogenic enzyme, in tumor progression. Thymidine phosphorylase (TP), an enzyme involved in pyrimidine metabolism . It is identical with an angiogenic factor, platelet-derived endothelial cell growth factor . The degradation product of thymidine generated by TP activity, has both angiogenic and chemotactic activity. Inhibition of TP activity and function appears to be a promising approach for the chemotherapy of various tumors.[Akiyama et al][14]

Study conducted on human cervical carcinoma cell lines to find there expression of thymidine phosphorylase and invasion

potentials. Study revealed that thymidine phosphorylase gene and protein expression levels in cervical carcinoma cell lines were closely related to the number of cells that migrated and invaded. [Masatsugu ueda et al][11]

X-ray irradiation also up-regulated Thymidine phosphorylase expression in several human cancer xenografts. A single-dose local irradiation at 5 Gy increased dThdPase levels by up to 13-fold at 9 days after the irradiation.the concluded that Combined modality treatment of cancer patients with cape-citabine and X-ray irradiation would have greater potential usefulness . [Sawada N et al][9]

A study with capecitabine, in locally advanced squamous cervical cancer with radiotherapy and cisplatin . In this study patients were treated with cisplatin weekly at 40mg/m^2, concurrently with radiotherapy and oral capecitabine daily.Two doses of capecitabine were studied 300 mg/m2 bid (cohort 1) and 450 mg bid (cohort 2).patient received whole pelvis EBRT dose of 45Gy in 25 fractions at 1.8Gy per fraction, followed intracavitry brachytherapy with doses between 24 to 30Gy to point A. diarrhoea and myelosuppression were the main toxicities in the study . Progression-free survival at 12 months was 69.2%, and

49.2% at 24 months.the over all survival was 57% at 24 months.the recommended dose of capecitabine in this study was 300mg/$m^{2.}$.[13]

A phase II study Capecitabine-Based Chemoradiotherapy with Adjuvant Capecitabine for Locally Advanced Squamous Carcinoma of the Uterine Cervix. In this phase II study**,** patients with FIGO stage IIB–IIIB cervical cancer received capecitabine, 825 mg/m2 twice daily (Monday–Friday), during radiation (45 Gy per 25 fractions external-beam radiotherapy and 26 Gy high-dose rate brachytherapy to point A, maximum 8 weeks), followed by six cycles of capecitabine, 1,000 mg/m2 twice daily (days 1–14 every 21 days). In this study the over all response rate was 88%and complete response was 80%.one year progression free survival rate 86% and over all survival rate were 86%.oniy 5% experienced capecitabine related grade 3 toxicities and only one patient had had hand foot syndrome.In this study the progression free survival rate at 23 months was 76% compared to GOG 120 study PFS rate was 67%[15].

The Capecitabine was also used in recurrent squamous cell carcinoma of cervix platinum based treatment. In a phase two trial of 22 patients Seventeen patients had prior radiotherapy, and 13

received a radiation sensitizer, whereas 2 patients underwent surgery exclusively and 3 patients had no prior treatment. Patient were treated with 50 mg/m2 of intravenous cisplatin on day 1 with 2500 mg/m2 oral capecitabine daily in 2 divided doses for 14 consecutive days in 21-day cycles. A median of 5 cycles was administered. the overall response rate was 31% with one CR and six PR. The study concluded cisplatin - capecitabine combination is a moderately tolerated and active regimen in advanced, persistent, or recurrent cervical cancer patients.[16]

AIM OF THE STUDY

To assess the immediate locoregional response rates of advanced cervical cancers treated with chemoradiation with weekly cisplatin and daily capecitabine followed by intracavitary brachytherapy.

MATERIALS AND METHODS

STUDY PERIOD

From March 2015 upto September 2015

ELIGIBILITY CRITERIA

Twenty four patients with locally advanced cancer cervix who satisfied the following eligibility criteria were included in this study.

1) Age: 30 - 60 years.

2) Performance status: Karnofsky performance score ~ 80

3) Disease stage: II B – III B

4) Histology: squamous cell carcinoma only

5) Haemoglobin > 10 gm%

6) Haematological parameters

   a. TC : 4000 and above / cubic mm
   b. PLT: 1 lakh and above / cubic mm
   c. RBC : 3 million and above / cubic mm

7) HIV negative

8) No history of treatment for the same complaints.

9) Informed consent of patients is a must.

EXCLUSION CRITERIA

1) Age : < 30 and > 60 years.

2) KPS : < 80

3) Hb : < 10 gm%

4) Histology other than squamous cell cancer

5) Disease stage: I, IIA & IV

6) Patients with history of other cancers

7) Patients with treatment history of same cancer.

8) HIV positve patients

9) Patients with past history of cardiac and hepatic disorders.

PRE TREATMENT WORK –UP

1) Complete clinical examination with emphasis on gynaecological examination.

2) Compete blood counts including Haemoglobin assay.

3) Biochemical investigations to assess renal function.

4) Cervix biopsy.

5) Cystoscopy.

6) Chest X -ray

7) CT/MRI abdomen and pelvis - to assess primary disease, local extension and visceral metastasis.

8) ECG.

9) HIV

INTRA TREATMENT ASSESSMENT

- Haemogram once a week to make sure that all patients had a TC of at least 4,000, a platelet count of 1,00,000 and a Hb status of 10 gm % before every chemotherapy schedule.

- Renal function tests once a week to rule out any altered renal functioning during treatment.

THERAPEUTIC PROTOCOL

STUDY DESIGN

All patients will be treated with external beam irradiation – 2 Gy *25# to whole pelvis to a total dose of 50 Gy along with weekly cisplatin 40mg and daily capecitabine 300 mg/sq.m. Patients will be assessed clinically for intracavitary brachytherapy and then will be treated with HDR remote after loading technique .

A) EBRT Equipment Co – 60 Phoenix for Teletherapy

B) ICA Equipment HDR Remote after loader Ir- 192 source HDR brachytherapy -

EBRT PROTOCOL IN STUDY

DOSE DETAILS

Total dose delivered	:	50 Gy
Dose /#	:	2Gy ,AP and PA portals, both portals treated daily
No of fractions	:	25
Total duration	:	5 weeks
Treatment days /week	:	5

Patients were assessed for ICA at the end of 25fractions of external beam radiation.

BED VALUE CALCULATIONS FOR EBRT

According to the linear –quadratic model the formula for calculating the biologically effective dose is

$$BED = Nxd\ [1+d/(\alpha/\beta)] - K[T-T0]$$

Where N - no of fractions

d - dose per fraction

α/β -dose at which the linear and quadratic cell kills are equal

k -constant (Dose required /day to counter act proliferation)

T - Over all treatment time

T_0 – Onset time for proliferation

In the conventional radiotherapy

Tumor –cancerous tissue in the cervix

BED =25 x 2 [1+2/10]-0.5[33-28]=57.5Gy

(α/β value of tumor in cervix-10 & k is constant -0.5)

Bladder- the late responding normal tissue

BED=25 x 2 [1 +2/4] =75 (α/β value of bladder-4)

Rectum – the late responding normal tissue

BED =25x 2 [1+2/3.87]=75.8 (α/β value of rectum-3.87)

TREATMENTPLANNING: EBRT

The whole pelvis including the cervix, vagina and parametria with the pelvic and iliac group of nodes was treated.

RT PORTAL MARGINS FOR EBRT

1. Superior	:	L4-L5 interspace (to include all the iliac and hypogastric nodes)
2. Inferior	:	If vagina is free - Lower margin of Obturator foramen. If vagina is involved - the entire vagina upto the introitus was included.
3. Lateral	:	2 cm lateral to bony pelvis.

SIMULATION AND TREATMENT DELIVERY

The treatment field was verified with PA simulator films in which the distal extension of the tumor was identified by placing a radio-opaque marker in the vagina. All patients were positioned in the prone position only with full bladder during external RT to exclude a greater extent of the small bowel from the treatment field. The AP portal was treated daily by gantry rotation of 180°.

B) ICA PROTOCOL

After teletherapy the patients were assessed for intra-cavitary application. Those found fit were subjected to high dose rate (HDR) Brachytherapy.

1) HDR BRACHYTHERAPY PROTOCOL

Technique	:	Remote afterloading with Iridium-192
No of #	:	TWO (1 week after EBRT –1 week apart)
Dose delivered to Point A	:	800cGy /# -2# (26Gy LDR equivalent)

SUMMATED DOSE: EBRT & HDR ICCA IN THE STUDY

Location	Dose
PT-A	83.2
PT-B	65Gy
Bladder	<80Gy
Rectum	<70Gy

CHEMOTHERAPY PROTOCOL

Drug	:	Cisplatin
Dose	:	40mg / m^2 -weekly
Schedule	:	Days1,8,15,22,29 of teletherapy
Total number of chemo cycles	:	5 cycles
Drug capecitabine Dose	:	300mg/m2 BD after food daily

RESULTS

After completing the full course of chemotherapy and radiation, the patients were analysed for tumour regression along with assessment for toxic reactions 6 weeks after completion of treatment.

The response was based on clinical assessment, CT /MRI scan. The response was graded as follows :

1) ***Complete Response:*** No clinicallydetectable lesion.

2) ***Partial Response:*** 50% regression of measurable tumour. No tumor area shows any progression No new area oflesion made out.

3) ***Static Response:*** No change in tumour size. No tumor area shows any progression. No new area of lesion made out

4) ***Progression :*** Increase in tumour size with treatment by >25% or Appearance of lesions or Tumor induced death Local control was defined as achievement of disease free period of at least 3 months after obtaining a complete response.

CASE ANALYSIS AND RESULTS

From March 2015 to august 2015 a total of 30 patients with previously untreated locally advanced cancer cervix fulfilled the criteria for inclusion in this trial. All thirty patients were treated with external beam radiation with concurrent chemotherapy followed by ICA with HDR brachytherapy (trial arm). All 30 patients were available for final analysis.

PATIENT CHARACTERISTICS

NUMBER OF CASES-30

1. Age Distribution

AGE(Years)	Number of cases
31-40	12(37.5%)
41-50	10(37.5%)
51-60	8(25%)

In this study we enrolled patients between 30-60 years of age. . Patients in the study were distributed in 4^{th} and 5^{th} decades.

2. Parity Status

No of pregnancies	Number of patients
>5 pregn	2 (8 %)
3-4 pregn	19 (80 %)
1-2 pregn	9 (12 %)

All the30 patients were multiparous with 55% of patients having 3-4 children

3. Performance Status-Karnofsky Scale

KPS scale	Number of patients
>90	14(47%)
80-90	16(53%)

The general status of the patients was evaluated based on KPS status. 47% of patients having performance status of above 90.

4. Haemoglobin Status

Hb	Number of patients
10-11 g/dl	8 (83 %)
11.1-12 g/dl	22 (17%)

All the patients had Hb values > 10 gms% at the start of study and was maintained with blood transfusions

5. Figo Staging Of Tumours

Clinical Stage	Number of Patients
II B	13 (43 %)
IIIB	17 (57 %)

All of the patients had either stage II B or III B disease, 43% had stage-IIB disease, 57% had stage III B disease.

6. Parametrlal Involvement

Parametrial Involvement	Stage	Number of patients
Unilateral	IIB	9 (38%)
	IIIB	-
Bilateral	IIB	4 (21%)
	III B	17 (41%)

More than 60% of patients had bilateral parametrial involvement.

8. HPE Based On Differentiation

Differentiation	No.of patients
Well differentiated	4 (13 %)
Moderately differentiated	19 (63 %)
Poorly differentiated	7 (23 %)

Only squamous cell cancers were included in this trial. Most of the patients had moderately differentiated squamous cell carcinoma.

ANALYSIS OF TREATMENT RESULTS

Analysis of immediate response was done 6 weeks after the end of planned treatment. This was done by clinical and radiological examination(CT/MRI abdomen and pelvis). All the 30 patients completed the prescribed treatments and were available for final evaluation of immediate response. The over all response of 100% seen at the end of external beam radiation was maintained after completion of treatment. None of the patients had static or progressive disease and there were no treatment-related deaths.

RESULTS OF STUDY

Stage	No of pts	CR		PR	
		No	%	No	%
II B	13	12	92	1	8
III B	17	15	88	2	12
Total	30	27	90	3	10

THE OVERALL COMPLETE RESPONSE- 90%

PARTIAL RESPONSE - 10%

Totally 27 patients in the study attained complete response (90% of the total patients in the arm). These included 12 out of 13 patients with stage IIB (92 % of all stage II B patients) and 15 out of the 17 patients with stage III B (88 % of all stage III B patients).

On evaluating the response based on patient and disease characteristics the following information was obtained

Response Vs Age Of Patient

Age	No.of patients(%)	
	CR	PR
31-40	12(100 %)	-
41- 50	9 (90 %)	1 (10 %)
51-60	6 (75 %)	2(25%)

COMPLETE RESPONSE AND AGE OF THE PATIENT

There was 100% (CR) in the age group(31-40)

Response Vs Performance Status (KPS)

KPS	No.of patients(%)	
	CR	**PR**
>90	14(100%)	-
80-90	13(86%)	3(14%)

Complete reponse and performance status of patient

In the present study patients with KPS of > 90 % had a CR of 100% and patients with a KPS of 80-90 had a CR of 86 %.

Response Vs Hb Status

Hb	No.of patients(%)	
	CR	**PR**
10-11 g/dl	6 (75 %)	2 (25 %)
11.1-12 g/dl	21 (95 %)	1(5%)

(P value=0.509-not significant)

Hemoglobin Level and Complete Response

The complete response rate increased with higher levels of hemoglobin. The trial benefited patients with Hb levels of > 11 gm % with a CR of 95% in this group.

Response Vs HPE

HPE	No.of patients(%)	
	CR	**PR**
Well differentiated	3 (75 %)	1 (25 %)
Moderately differentiated	17 (89 %)	2 (11 %)
Poorly differentiated	7 (100 %)	-

Complete Response and Tumor Grade

The 100% complete response was attained in poorly differentiated tumors

Response Vs Parametrial Involvement

P.M. involvement	No.of patients(%)	
	CR	**PR**
Unilateral 9 patients	9 (100 %)	-
Bilateral 2I patients	18 (86 %)	3 (14 %)

Complete Response and Parametrial Disease

Patients with unilateral disease had 100% complete response while those with bilateral disease had a complete response of 86%. Thus patients with unilateral disease are found to have better response rates .

Response Vs Disease Stage and Parametrial Involvement

Stage	Parametrial involvement	Complete response	Partial response
IIB	Unilateral	9(100%)	-
	Bilateral	3(75%)	1(25%)
IIIB	Unilateral	-	-
	Bilateral	15(88%)	2(12%)

Combined Influence of Stage and Parametrial Disease on Complete Response

1) Patients with stage IIB and unilateral parametrial disease had 100% CR.

2) Patients with stage IIB and bilateral parametrial disease had 75% CR.

3) Patients with stage III B and bilateral parametrial disease had 88 % CR

Number of Cycles Of Cisplatin Completed

Number of cycle of cisplatin	Number of patients
5 CYCLES	24
4CYCLES	5
3CYCLES	1

Number of Weeks of Capecitabine

No: of days of Capecitabine	Number of Patients
35 DAYS	25
28-35	4
21-28	1

TOXICITIES/ MORBIDITIES OBSERVED

Acute local toxicity is done by RTOG Acute morbidity scoring criteria.

SKIN REACTION

In this study 73% of the patients had Grade 1 skin reactions in the form of dry desquamation, decreased sweating. Another 20% had patchy moist desquamation whereas only 6% of the patient had grade 3 confluent moist desquamation.

MUCOSITIS

As expected there was high incidence of mucositis in this study. Nearly 56% of the study population developed grade 2 reactions in the form patchy mucositis. Also 20% had grade 3 confluent mucositis.There was delay in the brachytherapy schedule due to mucositis .This lead to prolongation overall treatment time.

The mucositis was managed by douching with diluted hydrogen peroxide and NSAIDs. Also Inj.Dexamethasone 8mg i.v. bid was given for 4-5 days.

Acute Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Skin Reactions	0	22 (73.66%)	6 (20%)	0	0	0
Mucositis	0	10 (33%)	17 (56%)	6 (20%)	0	0

RECTUM

In the study 40% of the patients of the patients developed grade 1 toxicity .20% of the patients grade 2 toxicity .patients were managed symptomatically with loperamide.

BLADDER

In the study about 36% of the patient had grade 1 toxicity as dysuria .symptoms were managed with adequate hydration.

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
RECTUM	12 (40%)	6 (20%)	0	0
BLADDER	11(36.6%)	0	0	0

SYSTEMIC TOXICITY

The treatment related systemic toxicity was assessed with CTCAE

V 4.03 and presented .

NAUSEA

83% of the study population developed loss of appetite grade 1 nausea during their treatment course.13% of the developed grade 2 nausea.

VOMITING

80% of the patients had grade 1(1 or 2 episode) of vomiting during chemotherapy mainly Cisplatin. Only 6% of the patients had grade 2(3 or 4 episodes) of vomiting managed by Oral Rehydration Salt and Inj.Ondansetron iv bid for 3 -5 days. Intravenous fluids were given whenever necessary.

DIARRHOEA

In the study diarrhoea was a major dose limiting toxicity .7% of the patients had grade 1 diarrhoea. Mostly the grade 1 diarrhoea is self-limiting, anti-motility drugs like Tab. Loperamide was used when needed. About 20% of the patients developed grade 2 diarrhoea. 13% of patient developed grade 3 diarrhoea requiring IV fluids and hospitalisation.

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	25 (83.33%)	4 (13.33%)	1 (3.33%)	0
Vomitting	24 (80%)	6 (20%)	0	0
Diahorrea	7 (23.3%)	6 (20%)	4 (13.3)	0

HAND FOOT MOUTH SYNDROME

The dreadful toxicity of Capacitabine hand foot mouth syndrome did not occur in any patients in this study.

HEMATOLOGICAL TOXICITY

ANAEMIA

In this study 22 patients had hemoglobin >11g % and 13% had reduction in their Hb levels during treatment between 9.5 - 11g%. 6% of the patients developed reduction in Hb levels to below 9g% and required Packed cell transfusion.All patients were given blood transfusion before there was fall in haemoglobin level.

Inspite of transfusion totally 19% had a fall in hemobglobin level requiring additional transfusion.

ANEMIA

Anemia	Number	Percentage
Grade 0	22	73%
Grade 1	4	13%
Grade 2	2	6%
Grade 3	0	0
Grade 4	0	0

LEUCOPENIA

In the study leucopenia was a major toxicity .4 patients developed grade 3 leucopenia (1000-2000) and were managed with G-CSF.for these patient the protocol was continued after improvement of WBC counts. 6 patients had grade 2 leucopenia .10 patients had grade 1 leucopenia. This can be attributed to the drug capectiabine.

NEUTROPENIA

In the study 2 patients developed grade 2 neutropenia

THROMBOCYTOPENIA

11 patients in the study developed grade 1 thrombocytopenia.

Acute Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Leucopenia	10	10	6	4	0
Neutropenia	26	2	2	0	0
Platelets	19	11	0	0	0

RENAL TOXICITY

All patients had normal renal function tests. Hence none of the patient developed renal toxicity.

DISCUSSION

More than 80% of cervical cancer cases are known to occur in developing countries and around 60 – 80% of cervical cancer cases in india present in a locally advanced stage.In india most the cervical cancer cases are reported form poor socioeconomical status. Women form the back bone of family, cervical cancer erode the family socially and economically as the treatment period is long.

For eight decades, exclusive radiation was the standard of care in locally advanced cervical cancer. five randomized control trails including nearly 2000 patients demonstrated survival benefit with concomitant chemoradiation based on cisplatin. The findings from the five randomized trails were corroborated by a subsequent meta-analysis of 19 trials including 4,580 patients which showed an absolute survival benefit of 12% at 5 years . The overall survival of locally advanced cervical cancer patients is 70% which suggests that the therapeutic protocols can be improved .

There has been continuous efforts to improve the treatment results.There has been analysis of tumor characteristics which lead to poor results The common pattern of failure is local recurrence,

especially in bulky cervical cancers. The results treatment of recurrence with salvage surgery and chemotherapy the are poor.So strategies with combining newer chemotherapeautic agents with existing agents along with radiation which will yield the highest pelvic tumor control with acceptable toxicity thus tailoring to the patient needs.

ANALYSIS OF RADIATION PROTOCOL

In the concurrent setting in the management of pelvic malignancies, the recommended dose is 45Gy -50Gy. various studies reported in the literature have used Conventional Fractionation In The Management Of Cancer Cervix

ANALYSIS OF CHEMOTHERAPY PROTOCOL

Chemotherapy regimens used in the earlier studies are either weekly cisplatin or cisplatin/5FU. Since weekly cisplatin is accepted as the standard in the concurrent setting, we preferred to use weekly cisplatin 40mg for a total of five cycle along with another chemotherapeutic agent capecitabine

CAPECITABINE

Capecitabine oral prodrug of 5FU, antimetabolite acts as a potent radiosensitizer.. Its role in metastatic and recurrent cervical cancer has been studied. Capecitabine as a single agent

concurrently with radiation has been tried in cancer cervix as it has radiosensitizing effect and can be administered orally.

But the dose of Capecitabine when used concurrently is reduced to 300mg/m^2 twice daily. Also Capecitabine acts as a targeted therapy with its rate limiting enzyme thymidine phosphorylase expressed at higher levels in tumors with hypoxia, acidosis and low pH. This is the condition in most of the solid tumorsThus the concentration of Capecitabine in tumor cell is 2.9 times higher than the normal tissues, reducing normal tissue toxicity. This is proved in various pharmacokinetic studies and trials with only Capecitabine with conventional radiation.

Cisplatin and 5FU have been used in three weekly regimens in various trials and there has been increased toxicity due to 5FU and also 5FU needed intravenous administration and the efficacy of this regimen is it is less toxic compared to cisplatin and 5FU.This present study was formulated with the idea of using potent chemotherapy drug with radiosensitization which might have a better toxicity profile, better loco regional control with good response rates.

This study of concurrent chemoradiation with weekly cisplatin and capecitabine has shown better complete response of 90% this is higher compared to weekly cisplatin single agent trial which has complete response rate of 88% conducted in our department. There was no static or progressive disease in this study.

DISCUSSION OF TREATMENT RESULTS

The detailed analysis of the case results has enabled us to identify certain tumor / patient characteristics which alter the immediate therapeutic response.

VARIABLE		CR	PR
No. of patients = 30		**90%**	**10%**
Age	31-40yrs	100%	-
	41-50yrs	90%	10%
	51-60yrs	75%	25%
Stage	IIB	92%	8%
	IIIB	88%	12%
KPS	>90	14(100%)	-
	80-90	13(86%)	3(14%)
Parametrial involvement	Unilateral	100%	-
	Bilateral	86%	14%

As reported elsewhere in the literature we found parametrial involvement as an important factor which determine the response to treatment .In this study we found that the response rate for patient with bilateral parametrial involvement was comparatively less than unilateral parametrial involvement

FACTORS ASSOCIATED WITH MORE FAVOURABLE RESPONSE

1) ***Younger Age*** Younger age patients were better able to Withstand the chemoradiation schedule and also had good performance Status and they completed the treatment protocol without any break.

2) ***IIB Stage*** : In this study even though IIB patient showed better Response than IIIB. The IIIB patients benefitted much as there Complete response was 88%.

3) ***Performance Status:*** In this study patients with good Performance status KPS>90 responded well to the treatment Protocol as most of them were also in the younger age group.

4) ***Poorly Differentiated:*** As poorly differentiated histology is Sensitive to chemoradiation there was 100% complete response in this Study.

Tumor factor	**Complete response rate**	
	Well differentiated	**Poorly differentiated**
Grade	75%	100%

FACTORS ASSOCIATED WITH POOR RESPONSE

1) Age <50 yrs

2) Hb: <11 gms %

3) KPS: < 80

4) Bilateral parametrial involvement

5) Stage III B disease

HEMOGLOBIN STATUS DURING TREATMENT

Tumor factor	**Complete response rate**	
	10-11g/dl	**11.1-12g/dl**
Anaemia during treatment	75%	95%

In this study about 6 patient developed grade 2 leucopenia , 4 patient developed grade 3 leucopenia and grade 2 neutropenia in 2 patients. So in these patients further dose of capecitabine withheld after third week. Pelvic RT with two radiosensitizing drug about 56% of the study patient developed grade 2 mucositis and 20% developed grade 3 mucositis leading to breaks in treatment and prolongation of over all treatment time.

Also 20% of the patient developed grade 2 rectal toxicity and grade 2 diarrhoea, 13% of the patient developed grade 3 diarrhoea. So further dose of capecitabine could not be given in these patients. Other patient were able to complete the chemoradiation schedule. Thought the treatment related toxicity developed they were manageable.

There wasn't any treatment related death in this study.

Thus we see that the following factors have *benefit* from concurrent chemotherapy : Clinically observed results are better in

1) Younger patients

2) KPS>90

3) Stage IIIB

But these are not statistically significant due to small sample size. Comparison of immediate response rates of various studies with concurrent CDDP and radiation in locally advanced cancer cervix reveals that the immediate complete response rates of our study are comparable with other studies

COMPARISON WITH INTERNATIONAL STUDIES

Study by	No of patients	Chemo schedule	CR rates
Runowicz et.al 5	32	CDDP 20 mg/m2 from DI-5 every 21 days	91 %
Fields et al4	55	CDDP 20 mg/m2 from DI-5 every 21 days	87%
Calkins et.al13	30	CDDP 50 mg/m2 D1 -17 5 FU D2,3,4,5&18,19,20,21	-
Previous study	26	CDDP 40 mg/m2 Weekly	88%
Present study	30	CDDP 40 mg weekly with capecitabine300mg/m2 daily	90%

Comparison of responses of various studies in our institution over the past five years

Study	Radiation dose			Chemo Schedule	Complete response
	Whole pelvis	PM	Point A		
Hyper fractionated RT	50.4Gy	65Gy	82Gy	-	75%
Weekly cisplatin – Conventional RT	50Gy	60.Gy	76Gy	CDDP Weekly day – 1 of every week	88%
Concurrent chemo with conventionalRT	50Gy	60Gy	76Gy	CDDP 20mg /m2 D1-5 &D 21-25	90%
Hyper fractionated RT with Cisplatin and 5 FU	57.6Gy	65Gy	83Gy	CDDP D1&17 5 FU D2,3,4,5& D18,19,20,21	84%
Present study	50Gy	60Gy	76Gy	CDDP40mg Weekly with capecitabine 300mg/m2 daily	90%

CONCLUSION

In developing countries cervical cancer continues to be major health burden . in india majority of cervical cancer are diagnosed in locally advanced stage despite significant advancement in the treatment with radiation and chemotherapy ther is still room for improvement of results for bulky disease, in disease free survival and progression free survival ,with new chemotherapy agents along with standard chemoradiation with manageable toxicities .Additional chemotherapy agents was added in the study to achieve the highest possible response rate with manageable toxicity. However the results need to be tested in longer number of patients to arrive at conclusion.

BIBLIOGRAPHY

1) Whitney CW, Sause W, Bundy BN, et al. Randomised comparison of Fluorouracil plus Cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIb– IVa carcinoma of cervix with negative para-aortic nodes; a Gynaecologic Oncology Group and South West Oncology Group study. J Clin Oncol 1999;17: 1339– 48.

2) Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin based radiotherapy and chemotherapy for locally advanced cervical cancer. N Eng J Med 1999;340:1144– 53.

3) Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky Stage Ib cervical carcinoma. N Engl J Med 1999;340:1154–61.

4) Morris M, Eiffel PJ, Lu JD, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high risk cervical cancer. N Eng J Med 1999;340:1137–43

5) Eifel PJ, Winter K, Morris M, et al. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high risk cervical cancer: an update of Radiation Therapy Oncology Group Trial (RTOG) 90-01. J Clin Oncol 2004;22:872– 80.

6) Lukka H, Hirte H, Fyles A, et al. Concurrent cisplatin based chemotherapy plus radiotherapy for cervical cancer—A meta-analysis.Clin Oncol 2002;14:203–12.

7) Pearcey R, Brundage M, Drouin P, et al: Phase III trial comparing radical radiotherapy with and without cisplatin chemotherapy in patients with advanced squamous cell cancer of the cervix. J Clin Oncol 20:966-972, 2002

8) Schuller J, Cassidy J, Dumont T, et al. Preferential activation of capecitabine in tumor following oral administration to colorectal cancer patients. Cancer Chemother Pharmacol 2000;45:291– 7.

9) Sawada N, Ishikawa T, Sekiguchi F, et al. X ray irradiation induces thymidine phosphorylase and enhances the efficacy of Capecitabine (Xeloda) in human cancer Xenografts Clin Cancer Res 1999;5: 2948– 53.

10) Miwa M, Ura M, Nishida M et al. Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. Eur J Cancer 1998; 34: 1274–1281.

11) Kono A, Hara Y, Sugata S et al. Activation of 5′-deoxy-5-fluorouridine by thymidine phosphorylase in human tumors. Chem Pharm Bull (Tokyo) 1983; 31: 175–178

12) Takebayashi Y, Yamada K, Miyadera K et al. The activity and expression of thymidine phosphorylase in human solid tumours. Eur J Cancer 1996; 32: 1227–1232

13) Phase one dose finding study of capecitabine (Xeloda\), radiotherapy and cisplatin in the treatment of locally advanced squamous cervical cancer Zuzana Stokesa, Paul Symondsb,*, Tim Habeshawc, Nick Reedc, Jorge Curtoc, Claire Joynsond, Steve Chand, Gynecologic oncology 97(2005) 790-795.

14) Akiyama S1, Furukawa T, Sumizawa T, Takebayashi Y, Nakajima Y, Shimaoka S, Haraguchi M The role of thymidine

phosphorylase, an angiogenic enzyme, in tumor progression Cancer Sci. 2004 Nov;95(11):851-7.

15) Capecitabine Based chemoradiotherapy with adjuvant capecitabine for locally advanced squamous cell carcinoma of the uterine cervix: Phase II Trial. Efren Domingo et al . the oncologist 2009, 14:828-834

16) Phase II Trial of Capecitabine and Cisplatin in Advanced, Persistent, or Recurrent Carcinoma of the Cervix. Hassan Errihani et al (Int J Gynecol Cancer 2011;21: 373Y377)

17) Hypoxia in Head and Neck Squamous Cell Carcinoma John Zenghong Li, Wei Gao, Jimmy Yu-Wai Chan, Wai-Kuen Ho, and Thian-Sze Wong Department of Surgery, The University of Hong Kong, Hong Kong ISRN Otolarynology,September 2012

18) . Sykes, N. J. Slevin, R. H. MacDougall, et al., “Results of a Phase I Study to Determine the Maximum Tolerated Dose of Capecitabine When Given Concurrently with Radical Radiotherapy in the Treatment of Squamous Cell Carcinoma of the Head and Neck,” Radiotherapy & Oncology, Vol. 71,

No. 1, 2004, pp. 81-84. Int J Radiat Oncol Biol Phys. 1993 Nov 15;27(4):871-8.

19) Weekly cisplatin plus external beam radiotherapy and high dose rate brachytherapy in patients with locally advanced carcinoma of the cervix. Souhami L1, Seymour R, Roman TN, Stanimir GW, Trudeau M, Clark BG, Freeman CR.

ANNEXURES

A. LOCAL

a. Skin - RTOG acute morbidity grading criteria

Grade	Change
0	No change over base line
I	Follicules, faint or dull erythema, dry desquamation, epilation, decreased sweating.
II	Tender or bright erythema, patchy moist desquamation, moderate edema.
III	Confluent, moist desquamation other than skin folds, pitting edema.
IV	Ulceration, hemorrhage, necrosis.

Mucosa - RTOG acute morbidity grading criteria

Grade	**Change**
0	No change
I	Erythema
II	Patchy mucositis.
III	Confluent mucositis.
IV	Ulceration.

a. Bladder - RTOG Acute morbidity grading criteria

Grade	Change
0	No change
I	Frequency of micturition nocturia twice that of pre-treatment frequency. Dysuria needing medication.
II	Frequency of micturition nocturia less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anaesthetic.
III	Frequency with urgency and nocturia hourly or more frequent. Dysuria, urgency, bladder spasm requiring regular narcotic. Gross haematuria with *I* without clot passage.
IV	Haematuria requiring transfusion. Acute bladder obstruction not secondary to clot passage. Ulceration or necrosis.

. Rectum - RTOG acute morbidity grading criteria

Grade	Change
0	No change
I	Increased frequency or change in bowel habits, rectal discomfort not requiring medication.

II	Diarrhoea requiring para-sympatholytic drug. Mucous discharge, rectal I abdominal pain requiring medication.
III	Diarrhohea requiring parenteral support, mucous or bloody discharge requiring sanitary pads
IV	Acute / sub- acute obstruction, fistula or perforation, GIT bleeding requiring transfusion. Abdominal pain, tenesmus requiring tube decomoression or bowel diversion.

e. Small bowel- RTOG acute morbidity grading criteria

Grade	**Change**
0	No change
I	Anorexia with 5% weight loss from base line. Nausea, abdominal pain not requiring medication
II	Anorexia with 15% weight loss from base line. Nausea and vomiting requiring medication.
III	Anorexia with> 15% weight loss from base line requiring NG tube or parenteral support. Severe abdominal pain despite medication. Haematemesis, melena or abdominal distension.
IV	Ileus, sub-acute obstruction, perforation. GIT bleeding requiring transfusion. Abdominal pain requiring tube decompression or bowel diversion.

HEMATOLOGIC TOXICITY

Grade	0	1	2	3	4
HEMATOLOGIC WBC (X 1000)	>=4.0	3.0 - <4.0	2.0 - <3.0	1.0 - <2.0	<1.0
PLATELETS (X 1000)	>=100	75 - <100	50 - <75	25 - <50	<25 or spontaneous bleeding
NEUTROPHILS	>=1.9	1.5 - <1.9	1.0 - <1.5	0.5 - <1.0	<0.5 or sepsis
HEMOGLOBIN (GM %)	>11	11-9.5	<9.5 - 7.5	<7.5 - 5.0	-

COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS CTCAE VERSION 4

GRADE	1	2	3	4
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake, tube feeding, TPN, or hospitalization indicated	-
Vomiting	1-2 episodes (separated by 5 minutes) in 24 hrs	3-5 episodes (separated by 5 minutes) in 24 hrs	>/=6 episodes (separated by 5 minutes) in 24 hrs,tube feeding,TPN or hospitalization indicated	Life-threatening consequences, urgent intervention indicated
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 -6 stools per da over baseline; moderate increase in ostomy output compared to baseline	Increase of =7 stools per day over baseline; incontinence; hospitalization indicated;severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated

INFORMATION TO PARTICIPANTS

Title: - **"Concurrent chemoradiation with weekly cisplatin and daily capecitabine followed by intracavitary brachytherapy in the management of advanced cervical cancers."**

Principal Investigator : Dr. Senthil Kumaran .M

Co-Investigator(if any) :

Name of Participant :

Site :

You are invited to take part in this research/ study/procedures/tests. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries or concerns.

What is the purpose of research?

Cisplatin is the cornerstone to most chemotherapeutic regimens used in cervical cancer therapy5 fluorouracil (5FU) may have compensated for the lower cisplatin dose intensity. Five-day infusions of 5FU are part of other chemoradiation regimens used to treat anal and oesophageal cancer, leading to improvement in local control and survival. However, the administration of these combination regimens requires either a 5-day hospital stay or insertion of a long line. The demand for hospital beds and the complications associated with intravenous lines make neither of these options ideal. Capecitabine is an orally available, tumour-selective fluoropyrimidine carbamate. It is bio-activated to 5 FU by three enzymatic reactions. The final reaction occurs selectively within the tumours by thymidine phosphorylase, thus minimizing the exposure of normal tissue to systemic 5 FU.

We have obtained permission from the Institutional Ethics Committee.

Study Design

Single arm prospective study

Study Procedures

The study involves evaluation of concurrent chemoradition with weekly cisplatin and daily capecitabine in locally advanced cancer cervix with CT/MRI Abdomen & Pelvis. The planned scheduled involve visits at _____,_____,____, and_____(days/ weeks) after your initial visit. You will be required to visit the hospital _____ number of times during the study.

At each visit, the study physician will examine you. Some [blood / urine /imaging/clinical examination other] tests will be carried out at each visit. [… … ml of blood will be collected at each visit. Blood collection involves prick with a needle and syringe.] These tests are essential to monitor your condition, and to assess the safety and efficacy of the treatment given to you.

In addition, if you notice any physical or mental change(s), you must contact the persons listed at the end of the document.

You may have to come to the hospital (study site) for examination and investigations apart from your scheduled visits, if required.

Possible risks to you – If any, Briefly mention

Possible benefits to you - If any, Briefly mention

Possible benefits to other people

The results of the research may provide benefits to the society in terms of advancement of medical knowledge and/or therapeutic benefit to future patients.

Confidentiality of the information obtained from you

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical history). By signing this document, you will be allowing the research team investigators, other study personnel, sponsors, Institutional Ethics Committee and any person or agency required by law like the Drug Controller General of India to view your data, if required.

The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

How will your decision to not participate in the study affect you?

Your decision not to participate in this research study will not affect your medical care or your relationship with the investigator or the institution. You will be taken care of and you will not loose any benefits to which you are entitled.

Can you decide to stop participating in the study once you start?

The participation in this research is purely voluntary and you have the right to withdraw from this study at any time during the course of the study without giving any reasons. However, it is advisable that you talk to the research team prior to stopping the treatment/discontinuing of procedures etc.

Signature of Investigator | Signature of Participant

Date | Date

INFORMATION SHEET

- You have been accepted by the Department of Radiotherapy to enrol into the study **"Concurrent chemoradiation with weekly cisplatin and daily capecitabine followed by intracavitary brachytherapy in the management of advanced cervical cancers."**

- We are conducting a study on cervical cancers among patients attending Government General Hospital, Chennai.

- The purpose of this study is to find if adding daily capecitabine in concurrent chemoradiation in cervical cancers will have a better response rates and lower recurrences.

- We are selecting certain cases and if your case is found eligible, we may be performing extra tests and special studies which in any way do not decrease your chance of optimum treatment.

- The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

- Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

- The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of investigator Signature of participant

INFORMED CONSENT FORM

Title of the Study:

CONCURRENT CHEMORADIATION WITH WEEKLY CISPLATIN AND DAILY CAPECITABINE FOLLOWED BY INTRACAVITARY BRACHYTHERAPY IN THE MANAGEMENT OF ADVANCED CERVICAL CANCERS.

NAME OF THE PARTICIPANT:

NAME OF THE PRINCIPAL (Co – Investigator): DR. SENTHIL KUMARAN .M

NAME OF THE INSTITUTION: MADRAS MEDICAL COLLEGE

_____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in "Concurrent chemoradiation with weekly cisplatin and daily capecitabine followed by intracavitary brachytherapy in the management of advanced cervical cancers."

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. I have been explained about my rights and responsibilities by the investigator.
5. I have been informed the investigator of all the treatments I am taking or have taken in the past_____ months including any native (alternative) treatment.
6. I have been advised about the risks associated with my participation in this study.*****
7. I agree to cooperate with the investigator and I will inform him/her immediately if I suffer unusual symptoms. *****
8. I have not participated in any research study within the past _____month(s). *****
9. I have not donated blood within the past _____ months—Add if the study involves extensive blood sampling. *****
10. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital. *****
11. I am also aware that the investigator may terminate my participation in the study at any time, for any reason, without my consent. *****
12. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors,

regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.

13. I have understand that my identity will be kept confidential if my data are publicly presented
14. I have had my questions answered to my satisfaction.
15. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document

Name and signature / thumb impression of the participant (or legal representative if participant incompetent)

Name _____ Signature_____ Date_____

Name and Signature of impartial witness (required for illiterate patients):

Name _____ Signature_____ Date_____

Address and contact number of the impartial witness:

Name and Signature of the investigator or his representative obtaining consent:

Name _____ Signature_____ Date_____

ஆராய்ச்சி தகவல் தாள்

ஆராய்ச்சியின் பெயர்:

பெண்களின் கருப்பை வாயில் ஏற்படும் புற்றுநோய்க்கு வெளி கதிர்வீச்சு சிகிச்சையுடன் **வாரந்தோறும் சிஸ்பிளாட்டின் மற்றும் தினமும் கேப்சிடாபின்** ஆகிய புற்றுநோய்க்கான மருந்துகளை கொடுத்த பிறகு "பிரேகிதெரபி" எனப்படும் உள் கதிர்வீச்சு சிகிச்சை அளித்து புற்றுநோயை குணப்படுத்துவது பற்றிய ஆராய்ச்சி.

ஆராய்ச்சியாளர் பெயர்:

பங்கேற்பாளர் பெயர்:

சென்னை இராஜீவ்காந்தி அரசு பொது மருத்துவமனைக்கு வரும் புற்று நோயாளிகளிடம் கதிர்வீச்சு சிகிச்சைப் பற்றிய ஆராய்ச்சி .

பெண்களின் கருப்பை வாயில் ஏற்படும் புற்றுநோய்க்கு பல வகையான கதிர்வீச்சு சிகிச்சை முறைகள் உள்ளன.முதலில் வெளி கதிர்வீச்சு சிகிச்சையுடன் **வாரந்தோரும் சிஸ்பிளாட்டின் மற்றும் தினமும் கேப்சிடாபின்** ஆகிய புற்றுநோய்க்கான மருந்துகளை கொடுத்து புற்றுநோயின் அளவை குறைத்த பிறகு "பிரேகிதெரபி" எனப்படும் உள் கதிர்வீச்சு சிகிச்சை அளித்து புற்றுநோயை குணப்படுத்துவது பற்றி ஆராய்வது இந்த ஆராய்ச்சியின் நோக்கம்.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க விரும்புகிறோம்.இந்த ஆராய்ச்சியில் தீவிர கதிர்வீச்சு சிகிச்சை அளித்து சில சிறப்பு பரிசோதனைக்கு உட்படுத்தி அதன் தகவல்களை ஆராய்வோம்.இதனால் தங்கள் நோயின் ஆய்வறிக்கையோ சிகிச்சையோ பாதிப்பு எற்படாது என்பதை தெரிவித்துக் கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துகளை வெளியிடும் போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களின் பெயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த சிறப்பு பரிசோதனைகளின் முடிவுகளையும் நோயின் தன்மை பற்றியும் ஆராய்ச்சியின் முடிவின் போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

தேதி:

ஆராய்ச்சி ஒப்புதல் கடிதம்

கருப்பை வாய் புற்றுநோய்க்கு வெளி கதிர்வீச்சு சிகிச்சையுடன் **வாரந்தோறும் சிஸ்பிளாட்டின் மற்றும் தினமும் கேப்சிடாபின்** ஆகிய புற்றுநோய்க்கான மருந்துகளை கொடுத்து புற்றுநோயின் அளவை குறைத்த பிறகு "பிரேகிதெரபி" எனப்படும் உள் கதிர்வீச்சு சிகிச்சை அளித்து செய்யப்படும் ஆய்வு.

பெயர்: தேதி:

வயது: உள்/புற
நோயாளி எண்:

பால்: ஆராய்ச்சி சேர்க்கை
எண்:

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக எனக்கு விளக்கப்பட்டன.

எனக்கு விளக்கப்பட்ட விவரங்களை நான் புரிந்துகொண்டு எனது சம்மதத்தை தெரிவிக்கிறேன்.

எனக்கு புற்றுநோய் இருக்கும் பகுதியில் கதிர்வீச்சு சிகிச்சை செய்து கொள்ள சம்மதம்.

இந்த ஆராய்ச்சியில் பிறரின் நிர்ப்பந்தமின்றி என் சொந்த விருப்பத்தின் பேரில் பங்கு பெறுகிறேன்.இந்த ஆராய்ச்சியில் இருந்து நான் எந்நேரமும் பின்வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்து கொண்டேன்.

நான் கருப்பை வாய் பகுதியில் முற்றிய புற்று நோய் குறித்த இந்த ஆய்வுக்கான விவரங்கள் கொண்ட தகவல் தாளைப் பெற்றுக் கொண்டேன்.

எனக்கு இந்த ஆராய்ச்சியில் தீவிர கதிர்வீச்சு சிகிச்சை மற்றும் புற்றுநோய் மருந்துகள் பெற்றுக் கொள்ள சம்மதம்.

இந்த ஆராய்ச்சியினால் ஏற்படும் நன்மைகளையும் , சில பக்கவிளைவுகளையும் பற்றி தெளிவாக மருத்துவர் மூலம் தெரிந்துகொண்டேன்.

நான் என்னுடைய சுயநினைவுடனும் மற்றும் முழு சுதந்திரத்துடனும் இந்த மருத்துவ ஆராய்ச்சியில் என்னை சேர்த்துக் கொள்ள சம்மதம் தெரிவிக்கிறேன்.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

தேதி:

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No. 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr.Senthil Kumaran M
Postgraduate M.D.(Radio Therapy)
Madras Medical College
Chennai 600 003

Dear Dr.Senthil Kumaran M,

The Institutional Ethics Committee has considered your request and approved your study titled **"Concurrent chemoradiation with weekly cisplatin and daily capecitabine followed by intracavitary brachytherapy in the management of advanced cervical cancers" No.34032015.**

The following members of Ethics Committee were present in the meeting held on 03.03.2015 conducted at Madras Medical College, Chennai-3.

1. Prof.C.Rajendran, M.D.,	: Chairperson
2. Prof.R.Vimala, M.D., Dean, MMC, Ch-3	: Deputy Chairperson
3. Prof.B.Kalaiselvi, M.D., Vice-Principal, MMC, Ch-3	: Member Secretary
4. Prof.R.Nandini, M.D., Inst.of Pharmacology, MMC	: Member
5. Prof.P.Ragumani, M.S., Professor, Inst.of Surgery, MMC	: Member
6. Prof.Md.Ali, M.D., D.M., Prof. & HOD of Medl.G.E., MMC	: Member
7. Prof.K.Ramadevi, Director, Inst.of Biochemistry, MMC	: Member
8. Prof.Saraswathy, M.D., Director, Pathology, MMC, Ch-3	: Member
9. Prof.S.G.Sivachidambaram, M.D.,Director i/c Institute of Internal Medicine, MMC, Ch-3	: Member
10.Thiru S.Rameshkumar, B.Com., MBA	: Lay Person
11.Thiru S.Govindasamy, B.A., B.L.,	: Lawyer
12.Tmt.Arnold Saulina, M.A., MSW.,	: Social Scientist

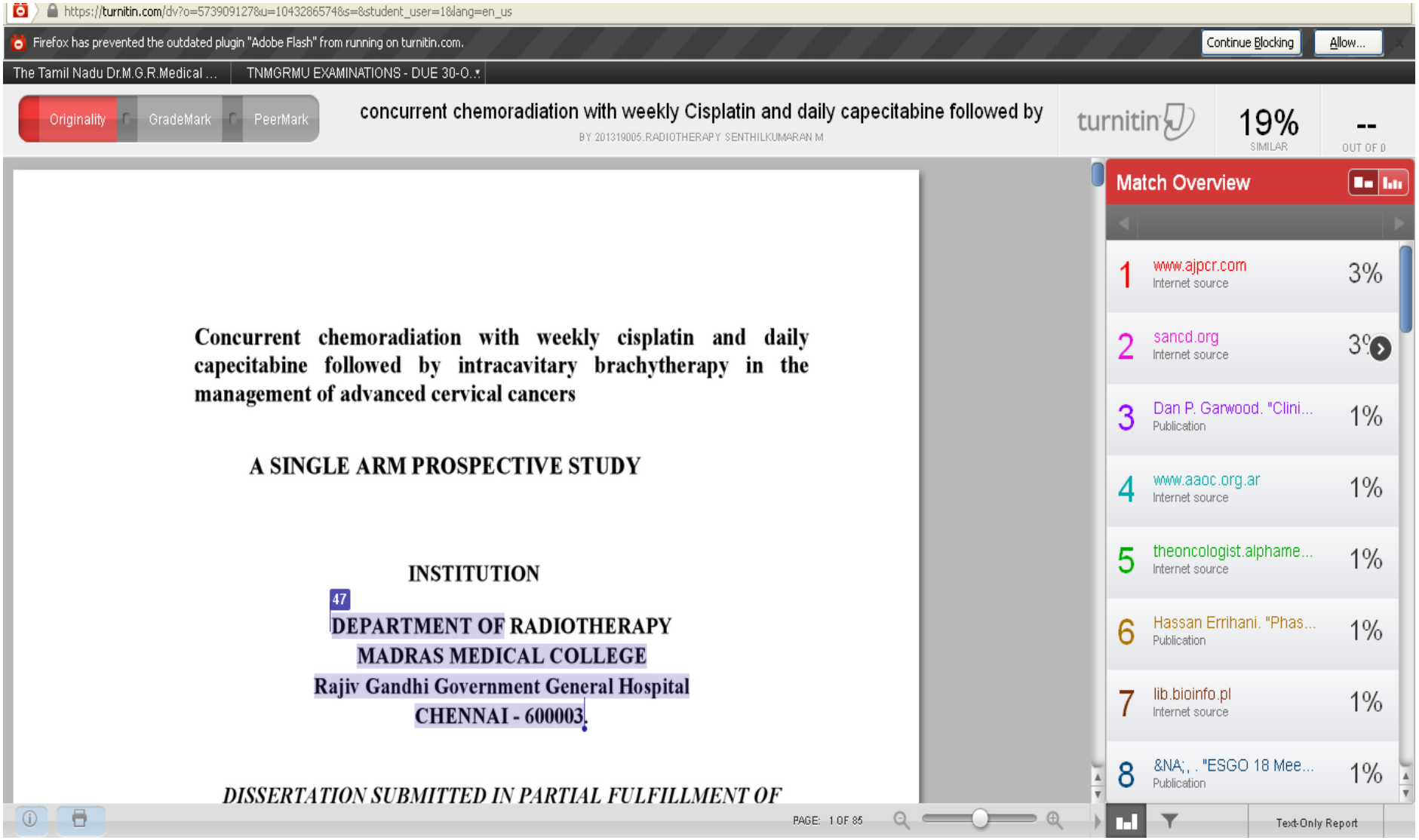
We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

8/3/15

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

Member Secretary, Ethics Committee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